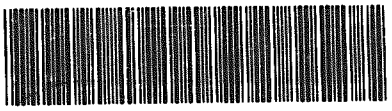
CHEMICAL MANUFACTURERS ASSOCIATION

LANGLEY A. SPURLOCK, PH.D., CAE
VICE PRESIDENT
CHEMSTAR

August 2, 1996



Document Processing Center (TS 790)
Office of Pollution Prevention and
Toxic Substances
U.S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attention: 8(e) Coordinator

Dear Sir or Madam:

The information below is submitted in accordance with the EPA's interpretation of Section 8(e) of the Toxic Substances Control Act by the Chemical Manufacturers Association Oxo Process Panel on behalf of the following producers of ethyl acetate: BP Chemicals, Inc., Eastman Chemical Company, Hoechst Celanese Corporation and The Monsanto Company.

DuPont Haskell Laboratories, under contract with the Panel, is conducting a study required under the Testing Consent Order for neurotoxicity testing on ethyl acetate (60 FR 4516, Jan. 23, 1995). The Panel does not believe that the data from the Haskell study constitutes a substantial risk. Nevertheless, this submission is intended to discharge any 8(e) responsibilities that might exist, and should be processed in accordance with the EPA's "substantial risk" procedures.

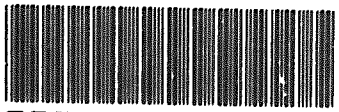
The information detailed below arises from microscopic pathological evaluations made following a 90-day vapor inhalation study with ethyl acetate (CASRN 141-78-6) in the rat:

> Minimal to moderate degeneration of the nasal olfactory mucosa was observed in males and females exposed to 350 ppm, 750 ppm, and 1500 ppm ethyl acetate and was considered to be compound related. This effect was observed at all exposure concentrations for both sexes and increased in incidence and severity with increasing exposure concentrations. Olfactory degeneration was generally limited to the dorsal and anterior regions of the nose.

This information should be considered preliminary. The final report will be submitted to the Agency as soon as it is available.

If you have any questions regarding this letter, please contact Barbara O. Francis, Manager of the Oxo Process Panel, at 703/741-5609.

Sincerely,



DuPont HLR

90-DAY INHALATION TOXICITY STUDY WITH <> IN RATS

Report <>. Pathology

Mortality, Organ Weight Data, Gross Observations, and Microscopic Findings

Date

Reported by: _____ _____

John F. Hansen, D.V.M., Ph.D.
Diplomate, A.C.V.P.
Staff Pathologist

Peer Reviewed by: _____ _____

<Randy>
Diplomate, A.C.V.P.
Staff Pathologist

Working Copy

REPORT <> Pathological Evaluations

Materials and Methods

Ten rats/sex designated for the 90-day clinical pathology examination from the control (0 ppm) and high concentration (1500 ppm) groups, and all surviving rats from the low (350 ppm) and intermediate (750 ppm) concentration groups were sacrificed by carbon dioxide anesthesia and exsanguination and necropsied after approximately 90 days on study.

Liver, kidneys, lungs, heart, spleen, brain, adrenal glands, testes (right), and ovaries from rats sacrificed by design at the end of the exposure period were weighed wet at necropsy. All rats on study were given a complete gross examination and representative samples of the following tissues were saved at necropsy: liver, kidneys, lungs, heart, skeletal muscle, spleen, aorta, brain (cerebrum, midbrain, cerebellum, medulla/pons), spinal cord (cervical, thoracic, lumbar), stomach, duodenum, jejunum, ileum, pancreas, cecum, colon, rectum, mesenteric lymph node, salivary glands, mandibular lymph node, harderian glands, exorbital lacrimal glands, thymus, adrenal glands, sciatic nerve, pituitary gland, thyroid gland, parathyroid glands, trachea, esophagus, pharynx/larynx, eyes, skin, mammary glands (female), ovaries, uterus, vagina, urinary bladder, prostate, seminal vesicles, testes (right), femur (including joint), sternum, bone marrow (femur, sternum), nose (4 sections) and selected gross lesions. Gross lesions which were diagnosed at necropsy and for which microscopic examination was not appropriate (e.g., fluid, ruffled fur, missing anatomic parts) were generally not collected. Selected gross lesions for which a microscopic diagnosis would not be additive (e.g., osteoarthritis, pododermatitis, chronic dermatitis of the tail, urinary calculi, and deformity of the teeth, toe, tail, or pinna) were saved but were generally not processed for microscopic evaluation.

All tissues were fixed in 10% neutral buffered formalin except testes, and eyes which were fixed in Bouin's solution. The lungs were inflated with 10% neutral buffered formalin after weighing.

All tissues, including selected gross lesions, collected from rats in the high-concentration and control groups that were sacrificed at the end of the exposure period and from early death rats (found dead, accidentally killed, sacrificed in extremis) during this period, were processed, embedded in paraffin, cut at a nominal thickness of 5 micrometers, stained with hematoxylin and eosin (H&E) and examined microscopically. Nose, pharynx/larynx, liver, kidneys, lungs and selected gross lesions from rats in the low- and intermediate-concentration groups were also processed to slides and examined microscopically.

Mean final body weights and mean absolute and relative (to body and to brain weight) organ weights were analyzed by one-way analysis of variance (ANOVA). Pairwise comparisons

between treated and control groups were made with Dunnett's test. The Bartlett's test for homogeneity of variances was performed on organ weight data and, if significant was followed by nonparametric procedures. Except for Bartlett's test ($p < 0.005$), significance was judged at $p < 0.05$.

See MATERIALS AND METHODS section <>. of the main report for the procedures used in this portion of the study.

Mortality (Tables <> and <>)

There were no compound-related deaths. One 750 ppm male rat was sacrificed in extremis due to a fractured tibia.

Organ Weights (Tables <> to <>, Appendix <>)

Results of Bartlett's test indicated that parametric procedures were required for some organ weights, as indicated in the organ weight tables. There were no compound-related effects on organ weights of rats exposed to the test substance.

The mean absolute and relative (to brain) spleen weights and the mean relative (to body) adrenal weight were significantly lower and higher than control weights, respectively in the 1500 ppm group males, and were considered to be secondary to lower body weight in this group. In females the mean absolute and relative (to brain) liver (1500 ppm) and spleen (1500 ppm) weights were significantly lower, and the mean relative (to body) kidney (750 and 1500 ppm), lung (1500 ppm), and adrenal (1500 ppm) weights were significantly higher than their respective control weights, and were all considered to be secondary to lower body weight in these groups.

Gross Observations (Tables <> to <>, Appendices <>)

There were no compound-related gross observations. All gross observations, except for the tibial fracture, were considered to be spontaneous lesions that occur sporadically in this strain and age of rat. The tibial fracture was considered to be an accidental injury.

Microscopic Findings (Table <> to <>, Appendix <>)

Minimal to moderate degeneration of the nasal olfactory mucosa was observed in males and females and was considered to be compound-related. This lesion was observed in all test levels of both sexes and increased in incidence and severity with increasing exposure concentrations. Olfactory degeneration was generally limited to the dorsal and anterior regions of the nose.

Other microscopic lesions were considered to be spontaneous lesions that occur sporadically in this strain and age of rat.

Discussions and Conclusions

The only primary compound-related pathology finding in this study was degeneration of the nasal olfactory mucosa in males and females at all test concentrations.

Under the conditions of this study, based on pathology, there was no NOEL established.

HN-21058
HC-8
MR-10502

INHALATION TOXICITY STUDY WITH H-21058

TABLE (Continued)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN MALE RATS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION:	I	III	V	VII
		CONCENTRATION (PPM):	0.0	350	750	1500
		NUMBER IN GROUP:	10	10	10	10
TESTES			10	0	1	10
FEMUR (INCLUDING JOINT)			10	0	1	10
STERNUM			10	0	1	10
BONE MARROW			10	0	1	10
NOSE I & II			10	10	10	10
DEGENERATION, OLFACTORY MUCOSA			-	3 (1.0)	10 (2.2)	10 (2.6)
INFLAMMATION, ACUTE			-	1 (1.0)	1 (2.0)	2 (1.5)
NOSE III & IV			10	10	10	10
DEGENERATION, OLFACTORY MUCOSA			-	-	6 (1.0)	10 (1.6)
OTHER			0	0	1	0
EPIDIDYMIDES: NOT REMARKABLE			-	-	1	-
CAUSE OF DEATH			10	10	10	10
SACRIFICED BY DESIGN			10	10	9	10
TIBIAL FRACTURE (DIAGNOSED AT NECROPSY)			-	-	1	-
MICROSCOPIC COMMENTS			0	0	0	0

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- o LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. DOUBLE DIGIT NUMBERS ARE EXPRESSED VERTICALLY, FOR EXAMPLE: (,1, ,1,1) MEANS NO LESIONS (-,0,6,1,5) WERE GRADED 'PRESENT", 10 LESIONS WERE "MINIMAL", 6 LESIONS WERE "MILD", 11 LESIONS WERE "MODERATE", AND 15 LESIONS WERE "SEVERE".

HN-21058
HC-8
MR-10502

INHALATION TOXICITY STUDY WITH H-21C58

TABLE (Continued)
INCIDENCES AND LESION GRADES OF MICROSCOPIC OBSERVATIONS IN FEMALE RATS

TISSUE/LESION	LESION GRADES (P,1,2,3,4)	GROUP DESIGNATION: CONCENTRATION (PPM): NUMBER IN GROUP: II 0 10	IV 350 10	VI 750 10	VIII 1500 10
MAMMARY GLANDS		10	0	0	10
OVARIES		10	0	0	10
UTERUS		10	0	0	9
VAGINA		10	0	0	9
URINARY BLADDER		10	0	0	9
FEMUR (INCLUDING JOINT)		10	0	0	10
STERNUM		10	0	0	10
BONE MARROW		10	0	0	10
NOSE I & II DEGENERATION, OLFACTORY MUCOSA		10 -	10 5 (1.0)	10 10 (1.9)	10 10 (2.5)
NOSE III & IV DEGENERATION, OLFACTORY MUCOSA		10 -	10 -	10 3 (1.3)	10 10 (1.4)
OTHER					
CAUSE OF DEATH SACRIFICED BY DESIGN		0 10 10	0 10 10	0 10 10	0 10 10
MICROSCOPIC COMMENTS		0	0	0	0

NOTES:
- o THE NUMBER OF ORGANS EXAMINED FOR EACH GROUP IS UNDERLINED.
- o LESION GRADES: P = PRESENT; 1 = MINIMAL; 2 = MILD; 3 = MODERATE; 4 = SEVERE.
- o LESION GRADES CORRESPOND BY POSITION WITH THE NUMBERS IN PARENTHESES, WHICH INDICATE HOW OFTEN EACH GRADE WAS OBSERVED. DOUBLE DIGIT NUMBERS ARE EXPRESSED VERTICALLY, FOR EXAMPLE: (,1, ,1,1) MEANS NO LESIONS (-,0,6,1,5) WERE GRADED "PRESENT", 10 LESIONS WERE "MINIMAL", 6 LESIONS WERE "MILD", 11 LESIONS WERE "MODERATE", AND 15 LESIONS WERE "SEVERE".